Division of Digestive Diseases and Nutrition

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Division of Digestive Diseases and Nutrition
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BARIATRIC SURGERY CLINICAL RESEARCH CONSORTIUM

FY 2003 Action

This RFA will invite applications for establishment of a Bariatric Surgery Clinical Research Consortium focusing on the development of an infrastructure to promote clinical research on bariatric surgery and its role in the understanding and treatment of obesity and its complications. Bariatric surgery involves reducing the size of the gastric reservoir, with or without a degree of associated malabsorption, with a goal of inducing weight loss among patients with extreme obesity. The objective of this Request for Applications (RFA) is to establish and maintain the infrastructure required for a Bariatric Surgery Clinical Research Consortium consisting of a group of interactive Clinical Centers (CCs) and a Data Coordinating Center (DCC). The goal of the Bariatric Surgery Clinical Research Consortium is to facilitate coordinated clinical, epidemiological, and behavioral research in the field of bariatric surgery, including development of a database to collect information from participating clinical centers. This will be a one-time solicitation to support a Clinical Research Consortium for five years.

Background

Obesity is increasing at alarming rates in the U.S., with more than 25 percent of adult Americans now considered obese (BMI>30). Of even more concern, there are large increases in the prevalence of higher levels of obesity (Class II, BMI 35-39.9 and Class III BMI >40). In some minority populations, such as African American women ages 40 to 60, the percentage of individuals with a BMI>40 exceeds 10 percent. Along with this increase in the prevalence of obesity has come a rise in the incidence and prevalence of obesity-related co-morbid conditions, such as type 2 diabetes. Although prevention of overweight and obesity remains the primary public health goal, more effective treatments for those who are already obese are crucial.

Numerous studies have shown that obesity treatments using behavioral therapy to improve diet and physical activity levels can lead to weight losses of approximately 5 to 10 percent over four to six months. Such weight losses result in improvements in obesity-related co-morbidities, such as hypertension, dyslipidemia, hyperinsulinemia, and progression to diabetes. However, these improvements are not maintained if weight is regained, and in a majority of cases, rebound in weight gain above the pre-intervention weight is the ultimate outcome. Therefore, better means to induce substantial weight loss in the extremely obese population, as well as to maintain weight loss over the longer term, are treatment goals. The most effective means currently available to induce substantial weight loss, with long-term maintenance of much of that weight loss, is through bariatric surgery.

A 1991 NIH Consensus Conference found that gastric restrictive or bypass surgery could be considered in well-informed and motivated patients with severe obesity (BMI>40) or less severe obesity (BMI>35) with high-risk co-morbid conditions. It was noted that insufficient data were available on which to base recommendations for patient selection using objective clinical features alone, and that additional research was needed to determine predictive factors. Long-term psychosocial effects of bariatric surgery were also unknown.

Since 1991, bariatric surgical procedures have become established modalities in the treatment of extreme obesity. It is estimated that 40,000 bariatric surgical procedures were carried out in the

U.S. in 2001, with an estimated 86,000 procedures projected for 2002. The two most frequently performed procedures are Roux-en-Y gastric bypass and vertical banded gastroplasty. Recent evidence suggests that weight loss is greater and regain less with the gastric bypass procedure. However, this increased effectiveness comes at the cost of increased adverse events, such as "dumping" syndrome, micronutrient deficiencies, and increased need for monitoring. Although intraoperative and postoperative mortality is low, morbidity is not infrequent. Early morbidity includes complications such as wound infection, staple line failure, dehiscence, venous thrombosis, and pulmonary embolism, while longer-term complications include stomal ulcerations and/or stenosis, micronutrient deficiencies, "dumping" syndrome, and psychosocial dysfunction. Laparoscopic bariatric surgery is becoming increasingly common, and both restrictive and malabsorptive procedures are carried out laparoscopically in some centers. In addition, some surgeons perform surgical procedures with greater malabsorptive components on selected patients, including biliopancreatic diversion, with or without duodenal switch, gastric bypass with extended limb lengths, etc., with an increased risk of protein-calorie malnutrition and other complications. Laparoscopic adjustable gastric banding is also increasing in popularity, although concerns have been raised about inadequate weight loss. Few systematic data are collected regarding risks, benefits, or outcomes with differing procedures or techniques.

Although systematic long-term follow-up across multiples sites is lacking, individual researchers have published case series with excellent follow-up. These studies suggest that bariatric surgery can have a long-lasting outcome on some co-morbid conditions, particularly type 2 diabetes. The Swedish Obese Subjects (SOS) is an ongoing non-randomized multi-center trial investigating the long-term effects of surgically induced weight loss on obesity-related morbidity and mortality, and may answer some, but not all, questions regarding the health impact of bariatric surgery. One limitation of this study is that most procedures were restrictive in nature, with more limited weight loss than is common with gastric bypass procedures.

Some of the research questions posed by the Consensus Panel in 1991 remain unanswered a decade later. These include the mechanisms whereby surgical treatment produces weight reduction, mechanisms of improvement in co-morbid risk factors or disease, safety and efficacy of bariatric surgery in defined subgroups, safety and efficacy of differing bariatric surgical procedures, and impact of bariatric surgery on subsequent pregnancy. The panel also noted the need for improved reporting of surgical results, and clearer outcomes assessment, including psychosocial outcomes. The importance of including meaningful control or comparison groups was also noted, although challenges in obtaining truly comparable groups were acknowledged.

In 2001, NIDDK, in conjunction with the American Society for Bariatric Surgery, sponsored a workshop on Research Considerations in Obesity Surgery, which provided an update on bariatric surgery and posed research questions that might be answered by future studies. Research topics proposed included the impact of bariatric surgery on subsequent pregnancy, impact of age on outcomes, assessing the impact of bariatric surgery on gastroesophageal function, and the effect of operations with greater malabsorptive potential on nutritional status. In May 2002, NIDDK convened a Working Group on Research in Bariatric Surgery that brought together investigators from a variety of disciplines to assist NIDDK in identifying areas of scientific opportunity pertaining to bariatric surgery and its impact on obesity and co-morbid conditions. A number of topics were identified as research opportunities, including using bariatric surgery as a model to

understand underlying pathophysiology of obesity-related diseases, and evaluation of the safety and efficacy of bariatric surgical procedures, including their impact on weight loss, co-morbid conditions, psychosocial status, quality of life, and economic factors. Studies looking at both short-term and long-term outcomes were felt to be critical. The need for refining phenotyping to better predict outcomes, and hence improve risk/benefit ratio of an individual patient was also considered essential. A consortium of centers performing bariatric surgical procedures on large numbers of patients would permit collaborative studies in more basic areas, including studies on energy balance, nutrient absorption, physiology and metabolism, and the genetics of severe obesity. Establishing a bariatric surgery database, to collect hypothesis-driven data on multiple variables of clinical and scientific interest was considered a potential strength of such a collaboration, which could provide information on clinically important predictors and outcomes, as well as economic and quality of life data.

A Bariatric Surgery Clinical Research Consortium will accelerate clinical research and progress in understanding the pathogenesis of severe obesity and its complications, as well as in understanding the risks and benefits of bariatric surgery as a treatment modality. Use of standardized definitions, clinical protocols, and data collection instruments will enhance the ability to provide meaningful evidence-based recommendations for patient evaluation, selection, and follow-up care. Also, the Bariatric Surgery Clinical Research Consortium will help pool the necessary clinical expertise and administrative resources to facilitate the conduct of multiple and novel clinical studies in a timely, efficient manner. This, in turn, will promote rapid dissemination of research findings to health care professionals.

Research Goals and Scope

The objective of this RFA is to establish a Bariatric Surgery Clinical Research Consortium that will provide an infrastructure for the creation and maintenance of a bariatric surgery database, and for the development and implementation of pilot and feasibility studies, planning studies for larger clinical trials, and studies investigating the mechanisms of bariatric surgery in impacting appetite, nutrient absorption, energy expenditure, and obesity related co-morbid conditions including, but not limited to type 2 diabetes and pre-diabetes, non-alcoholic steatohepatitis, hypertension and cardiovascular disease. Studies that may assist in identifying predictive factors for successful weight loss and amelioration of co-morbid conditions in patients undergoing bariatric surgery procedures are encouraged, as are studies on psychosocial and behavioral predictors and outcomes, as well as on the economic impact of bariatric surgery.

HEPATOTOXICITY CLINICAL RESEARCH NETWORK (RFA DK-02-033)
http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-02-033.html

FY 2003 Action
This initiative invites applications for the establishment of a Clinical Research Network that will focus upon the elucidation of the clinical features and pathogenesis of drug and toxin-induced liver injury, a common cause of acute liver disease, morbidity and mortality. Drug and toxin-induced liver injury can be mild and transient, resulting merely in a transient elevation in serum aminotransferase levels, but also can be severe, protracted and even life-threatening, resulting in acute liver failure. Most severe adverse hepatic toxic reactions are unpredictable, idiosyncratic and uncommon. In addition, attribution of the hepatic injury to the medication can be unclear and complicated by the presence of other possible causes of liver disease. Liver injury from drugs is often not predicted by pre-clinical testing in laboratory animals and most medications that cause severe liver disease in humans cause little or no hepatic injury in animals. Furthermore, the increasing use of complementary and alternative medicines (CAM) has led to additional cases of toxin-induced liver disease that are often more challenging and confusing to evaluate. Complementary medications often consist of mixtures of herbs and other active compounds that may not be well characterized or studied.

These features make diagnosis of drug and toxin-induced liver injury difficult and analysis of the causes of hepatotoxicity limited. Yet drug-induced liver disease is becoming an increasingly important problem in medicine. With an increasing proportion of the U.S. population taking medications as well as CAM therapies, the clinical burden of hepatotoxicity is only going to worsen. Hepatotoxicity is the single, most common adverse drug reaction that leads to drug withdrawal and or refusal of approval by the Food and Drug Administration (FDA). Such withdrawals or refusals have enormous financial implications for the pharmaceutical industry and can result in the loss of availability of an effective therapy because of a rare occurrence of toxicity in a small proportion of patients who take the medication. The intent of this Request for Applications (RFA) is to establish and maintain the infrastructure required for a Hepatotoxicity Clinical Research Network consisting of a group of interactive Clinical Centers (CCs) and a Data Coordinating Center (DCC). The primary objective of the Hepatotoxicity Clinical Research Network is to develop standardized instruments to identify and fully characterize bona fide cases of drug, CAM and toxin-induced liver injury to allow for analysis of the epidemiology and clinical spectrum of hepatotoxicity and to obtain biological samples for study of the pathogenesis of hepatotoxicity using biochemical, serological and genetic techniques. The recent development of powerful methods of genetic analysis and pharmacogenomics promises to provide important insights into the mechanisms of drug actions and drug toxicities. These techniques require the availability of carefully defined cases of liver injury to both create and test hypotheses on metabolic pathways that predispose to liver injury. This initiative will expand our understanding of the mechanisms of drug and toxin-induced liver injury and provide the basis for more effective and safe medical therapies. This is a one-time solicitation to support a feasibility phase of a Hepatotoxicity Clinical Research Network for three years.

Background
Adverse drug reactions (ADRs) are an increasingly important clinical problem in medicine. ADRs are estimated to cause more than 100,000 deaths per year in the U.S. and, therefore, rank

among the ten most common causes of death. Up to 5 percent of all hospital admissions may be attributable to ADRs. Increased length of stay in hospital due to ADRs by two days can cost as much as $2,500 per patient. Drug-induced liver injury has been the most common type of ADR that has led to drug withdrawal or refusal of approval by the FDA. In surveys of acute liver failure in the U.S., drug-induced hepatotoxicity is the single leading cause.

The cause of acute liver injury due to medications, CAM therapies and toxins is often unknown, but in many situations genetic predisposition appears to play a leading role. The role of inheritable variations in predisposing to ADRs was shown by the correlation between drug responses and inherited deficiencies of metabolic enzymes such as pseudocholinesterase (butyrylcholinesterase) and glucose-6-phosphate dehydrogenase (G6PD). Genetic polymorphisms (variant alleles present at least in 1 percent of the normal population) are a source of genetic variation to drug responses.

Although the study of drug-induced liver abnormalities has centered on the involvement of pharmacokinetic factors (absorption, distribution, metabolism and excretion) there is increasing evidence that genetic variation in drug targets (pharmacodynamic factors: receptors, channels, enzymes, immune factors) might also predispose to hepatotoxicity. In addition, environmental factors such as disease, alcohol, smoking and diet might also be significant sources of variability, interacting with genetic factors.

Thus, predisposition to hepatotoxicity is likely to be multi-factorial, involving genes that interact with environmental factors. In a similar fashion to complex diseases, heterogeneity of gene variants may also interact to give rise to a similar pattern of injury. These factors of pathogenesis, coupled with the absence of predictable animal models, the lack of specific diagnostic tests, the inaccuracies of scoring scales for drug-induced liver toxicity and the unpredictable, idiosyncratic nature of most drug-induced liver toxicity, has hampered the systematic analysis and study of hepatotoxicity.

To begin to analyze the pathogenesis and genetic basis of drug and toxin-induced liver disease, it is first important to have unambiguously characterized cases of hepatotoxicity (phenotype) and carefully selected control subjects. Collection of well defined cases of hepatotoxicity are needed to engage in genetic profiling to establish phenotype-genotype correlations which might predict drug and toxin-induced hepatic injury. To address these issues and to determine the feasibility of prospectively collecting cases of drug, CAM and toxin-induced liver toxicity, a Hepatotoxicity Clinical Research Network is proposed. The primary objective of the Network is to develop operational diagnostic criteria, causality assessment instruments and strategies to identify and collect well defined cases of toxin-induced liver injury in a prospective manner that will permit careful collection of clinical information as well as serum, DNA and tissue/samples for biochemical, pharmacological and genetic analyses.

Research Goals and Scope

The objective of this RFA is to establish a Hepatotoxicity Clinical Research Network that will accelerate advances in the understanding and prevention of drug, CAM and toxin-induced liver toxicities. This RFA will fund the development of a protocol and study design and a feasibility phase of the implementation of the study. The Network will have two phases. The first phase

will be the development of working definitions for drug-induced liver toxicity, diagnostic algorithms, a causality assessment protocol or instrument, an overall study design to identify cases, a manual of operations for clinical data and specimen collection, and an adequate patient consent form. This phase will extend for up to 12 months from the award start date and will conclude when there is a full-scale study design, data collection forms, a manual of operations and patient consent forms that have been approved by local Institutional Review Boards.

The second phase will start with the implementation of the operating procedures and enrollment of patients and control subjects and the capture of data and samples. This phase will last for 24 months. During this phase, patients will be identified and studied, data collected and serum, DNA and tissue specimens collected. During this phase the NIDDK will assess the progress of the primary objectives of the Network and if appropriate, a second RFA will be issued to continue the Hepatotoxicity Clinical Research Network in a fully operational form, with proposals to initiate the genetic profiling studies aimed to determine the role of genetic variability in drug, CAM and toxin-induced liver toxicity.

As the Network accumulates clinical information it would provide the preliminary data and background for further investigator-initiated research in both clinical and laboratory areas of interest by providing reagents, specimens or opportunities to assess hypotheses on the pathogenesis, prevention or treatment of drug, CAM and toxin-induced hepatotoxicity.

The Network can also provide a focus of learning in hepatotoxicity and serve as a regional and national clinical resource for advice on hepatotoxicity.

PANCREATITIS: MECHANISMS, PREVENTION AND THERAPY

FY 2003 Action

This PA will solicit R01 and R21 applications to encourage experienced and new investigators to pursue basic and clinical investigations into the diagnosis, epidemiology, natural history, pathogenesis, treatment and prevention of acute and chronic pancreatitis and its sequelae.

Background

Pancreatitis is a syndrome that is characterized by pain associated with inflammation and damage to the pancreas. Relapsing or chronic pancreatitis can lead to exocrine and endocrine pancreatic insufficiency. Major causes of pancreatitis are alcohol, cholelithiasis, drug toxicity, and infections. In some cases there may be a genetic basis. However, a significant percentage of cases are idiopathic, in that no causative agent can be found despite extensive investigation.

Research Goals and Scope

This initiative will encourage further research in a number of areas.

- Basic studies of the organogenesis of the exocrine pancreas, the physiology and altered function of the ductal and acinar cells in both human and animal models.
- The creation of new animal models which exhibit acute or chronic pancreatitis.
- Studies aimed at the identification of the cellular and molecular events leading to the "preneoplastic" genetic changes that occur and predispose individuals to adenocarcinoma of the pancreas.
- Clinical studies of early detection and diagnosis, prognostication, prevention and treatment of acute and chronic pancreatitis.
- The pathogenesis, natural history, and management of patients with possible pancreatic sphincter of Oddi dysfunction, recurrent pancreatitis, or *pancreas divisum*.
- The clinical significance, natural history, and management of microlithiasis or "biliary sludge" in the pathogenesis of pancreatitis.

LIVER AND PANCREATIC DISEASE IN HIV INFECTION (PA-01-117)
http://grants1.nih.gov/grants/guide/pa-files/PA-01-117.html

FY 2003 Action
The purpose of this Program Announcement is to invite clinical and basic research applications that focus on the pathogenesis and therapeutics of the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. The co-infections targeted by this Program Announcement (PA) specifically include hepatitis B and hepatitis C, which are frequent causes of end-stage liver disease; a leading cause of death in HIV infected patients. Metabolic complications, involving the liver and pancreas, associated with the treatment of HIV infection include hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis (NASH) and pancreatitis, which are all important causes of morbidity in patients with HIV infection. The proposed studies should advance our understanding of the pathogenesis of liver and pancreatic disease in patients with HIV and/or metabolic complications of therapy. These advances should lead to enhanced medical management of individuals infected with HIV.

Background
The current initiative specifically targets hepatic and pancreatic co-morbidities in the context of HIV infection, and metabolic complications of antiretroviral treatment in support of basic and clinical research that addresses the significant emerging clinical issues of disease progression in patients with HIV infection.

Highly active antiretroviral therapy (HAART) has slowed the progression of HIV disease and decreased the rate of HIV-associated mortality. In the context of enhanced longevity for HIV patients, other co-morbidities, such as chronic liver disease and pancreatitis, can assume greater importance in the medical management of patients. Based on shared routes of transmission, HBV and HCV infection are common in HIV-infected patients. HIV infection has a significant effect on the natural history of HBV infection with co-infected individuals more likely experience severe liver disease. Individuals treated with lamivudine as part of their antiretroviral treatment more frequently fail treatment, resulting in the emergence of drug resistant strains of HBV. Several studies have also documented that HIV disease modifies the natural history of chronic HCV infection leading to an accelerated course of progression to end-stage liver disease and death. The accelerated course to end-stage liver disease has been suggested to be reduced from the two to four decade time-frame for HCV mono-infection to as little as five to six years in HCV/HIV co-infected patients. The result of the common occurrence of hepatitis and HIV co-infection and accelerated disease progression is the report that end-stage liver disease is now the leading cause of death in hospitalized HIV-infected patients.

The etiology and pathogenesis of enhanced progression to end-stage liver disease in HIV co-infected patients is unknown. Recent data have shown that hepatitis co-infection results in enhanced liver disease in individuals infected with HIV through enhanced severity of fibrosis, a higher frequency of cirrhosis and end-stage liver disease as well as increased deaths due to liver disease. The role of HCV quasispecies, the effects of immune deficiency on the course of hepatitis C, hepatotoxicity due to antiretroviral treatment, chronic HBV infection, immune restoration and HBV infection, and development of nonalcoholic steatohepatitis (NASH) as a

result of lipodystrophy have all been hypothesized to play a role in the enhanced liver disease seen in co-infected individuals. Additional research is needed to identify the mechanism(s) of pathogenesis and to identify therapeutic targets for treatment.

Research Goals and Scope

This initiative will support basic and clinical research in HIV co-infection and metabolic disease related to antiretroviral treatment. Areas of interest include but are not limited to:

- The elucidation of biological mechanism(s) that promote enhanced progression of liver disease in HIV-infected patients.
- A further elucidation of drug-induced hepatotoxicity associated with anti-retroviral treatment regimens.
- The identification of therapeutic targets and/or novel therapies for the treatment of liver disease in HIV-infected patients.
- The elucidation of synergy between HIV and HCV, resulting in enhanced liver disease.
- Enhanced knowledge of antiviral treatment failures of HBV/HIV co-infection and the emergence of HBV drug-resistant strains.
- Identify underlying liver disease, such as NASH, in combination with HIV infection and antiretroviral treatment, that progresses to end-stage liver disease.
- Therapeutics development for the enhanced medical management of patients with HBV/HIV or HCV/HIV co-infection or metabolic abnormalities due to antiretroviral treatment.
- Altered hepatic lipid metabolism due to antiretroviral treatment.
- HIV-associated pancreatitis and risk factors (hypertriglyceridemia, obesity and gallstones).
- The impact of liver transplantation on disease progression in select patients with co-infections with Hepatitis B or Hepatitis C.

ENDOSCOPIC CLINICAL RESEARCH IN PANCREATIC AND BILIARY DISEASES

FY 2003 Action

This program announcement encourages applications using the small grant (R03) mechanism in an attempt to encourage innovative clinical and epidemiological research into the role of Endoscopic Retrograde Cholangiopancreatography (ERCP) and other endoscopic and imaging techniques. Acute and chronic pancreatic and biliary diseases are common in the U.S. and account for considerable morbidity, mortality and health care costs. The spectrum of conditions includes those due to cancer of the exocrine and endocrine pancreas, gallstones, sludge, pancreatic and biliary malignancy, trauma, anatomic problems (*pancreas divisum*), alcohol and drugs, and idiopathic syndromes such as idiopathic pancreatitis and sphincter of Oddi dysfunction. The National Institutes of Health State of the Science Conference Statement on ERCP indicated that while ERCP and other advanced endoscopic and imaging techniques have gained widespread application in clinical practice, there is little evidence based on rigorous clinical trials to guide the use of advanced diagnostic and therapeutic technologies in clinical practice decisions.

Background

Diseases of the gallbladder, pancreas, and liver are conditions that are frequently encountered in clinical practice. Examination of the biliary and pancreatic ducts is often required for the appropriate diagnosis and management of patients with pancreatic and hepatobiliary diseases. Over the last three decades, the dramatic improvement of flexible endoscopes has established endoscopy as the primary method to diagnose and treat many pancreatic and biliary diseases.

Although ERCP first came into use about 30 years ago and has been applied to the diagnosis and management of a variety of gastrointestinal disorders, the value of ERCP relative to other means for diagnosing and treating these diseases has not been firmly established. Over the last two decades, there has been the development of new diagnostic and therapeutics tools—ultrasound, standard and helical computer tomography, magnetic resonance imaging (MRI), magnetic resonance cholangiography (MRCP), endoscopic ultrasound, and intraoperative cholangiography with potential usefulness in management of pancreatic and hepatobiliary diseases. Each of these tools has variable detail and accuracy. A State of the Science Conference on ERCP in diagnosis and therapy was held at the NIH on January 14-16, 2002 (http://consensus.nih.gov/cons/116/116_intro.htm). Several of the recommendations of the conference included the need to improve the quality of clinical trials for the study of pancreaticobiliary diseases as well as to evaluate ERCP and other and newer technologies in assessing pancreaticobiliary diseases.

The goal of this small grants program is to provide flexibility for initiating preliminary, short-term studies, thus allowing new ideas to be investigated in a more expeditious manner without stringent requirements for preliminary data. Such support is needed to encourage experienced investigators as well as new investigators to pursue new approaches, underdeveloped topics, or more risky avenues of research. If successful, these awards should lead to significant scientific advances in defining the role of ERCP and other advanced endoscopic interventional and imaging techniques in the prevention, diagnosis and management of pancreatic and biliary diseases.

Research Goals and Scope

This PAR will encourage clinical research in a number of areas:

- Comparisons of interventional endoscopic procedures *versus* interventional radiological approaches *versus* surgery for treatment of different complications of chronic pancreatitis.
- Studies of the role of endoscopic interventions for acute pancreatitis, chronic pancreatitis or its complications.
- Studies of the role of ERCP in sphincter of Oddi dysfunction (biliary or pancreatic sphincter).
- Clinical studies of early detection and diagnosis, prognostication, prevention and treatment of acute and chronic pancreatitis as well as pancreatic cancer
- The clinical significance, natural history, and management of microlithiasis or "biliary sludge" in the pathogenesis of pancreatitis.
- Clinical studies of the role of endoscopic and other advanced technologies in early diagnosis, staging or treatment of biliary or pancreatic malignancy; including but not limited to the collection of pancreatic juice for the chemical analysis, cytopathology, proteomics, and gene expression microarrays.
- Other studies of pancreatic and biliary diseases that compare ERCP, diagnostic imaging or surgical approaches.
- Studies to enhance and evaluate training for laparoscopic common bile duct exploration (and other surgical techniques) and to improve training for advanced endoscopy.
- Development of endoscopic and laparoscopic simulators and other new technologies to facilitate training, maintenance and objective assessment of procedural performance.

INTESTINAL FAILURE, SHORT GUT SYNDROME AND SMALL BOWEL TRANSPLANTATION (PA-02-163)
http://grants2.nih.gov/grants/guide/pa-files/PA-02-163.html

FY 2003 Action
This Program Announcement will solicit grant applications to study the pathogenesis, natural history, treatment and complications of intestinal failure and its therapies, including parenteral nutrition and small bowel transplantation. Intestinal failure, which is defined as reduced absorption of nutrients from the gastrointestinal tract resulting in the need for parenteral nutrition for survival, has many causes, including primary defects of intestinal epithelial absorption, motility disorders, and loss of large portions of the intestine due to surgical resection for congenital defects, necrotizing enterocolitis, ischemia, trauma, and inflammatory bowel disease. It is estimated that 20,000 individuals in the U.S. are supported by parenteral nutrition for intestinal failure and that the economic and quality of life burden for these patients is very high. A small fraction of these patients undergo small bowel transplantation, a treatment with significant morbidity, mortality, and high cost. Thus, new fundamental discoveries that lead to ways to prevent intestinal failure or its complications, to improve existing therapies, parenteral nutrition or small bowel transplantation, or to devise novel therapies, could lead to a significant improvement in quality of life and decreased cost of care for patients suffering from intestinal failure.

Background
The overall objective of this PA is to encourage basic and clinical research into intestinal failure, short gut syndrome and intestinal transplantation. There are many causes of intestinal failure, each of which has varying degrees of information regarding etiology and pathogenesis. Intestinal failure can be due to intrinsic diseases of the gastrointestinal tract or result from major loss or resection of the intestine (short gut syndrome). By definition, therapy for intestinal failure relies on parenteral nutrition, usually in conjunction with oral nutritional support. While some patients may survive indefinitely using parenteral and oral nutritional support, others suffer multiple complications, such as recurrent infection, dehydration, vascular thrombosis, or progressive liver disease that may result in death. A small number of patients with these complications may be rescued by small bowel transplantation, which itself is associated with numerous potential complications and requirement for lifelong immunosuppression.

Research Goals and Scope
The specific objectives of this PA are to encourage research addressing the overall problem of intestinal failure, which may include, but is not restricted to any of the following topics.

- Studies of the etiology and pathogenesis of intestinal failure where the cause is not well understood, especially necrotizing enterocolitis in infancy, congenital developmental defects, motility disorders, defects of transport such as microvillus inclusion disease, and early childhood inflammatory disorders of the gut.
- Studies of the genetic and molecular basis of gut development in animal models that may lead to novel insights into intestinal failure.
- Basic and clinical studies of gut adaptation to intestinal failure, including the role of nutrients, endogenous factors such as growth factors, intestinal flora, and therapeutic agents.

- Studies to define nutrient requirements, either oral or parenteral, necessary to maintain optimal health for patients with intestinal failure.
- Studies of the complications of intestinal failure and its therapy, particularly the etiology, diagnosis and treatment of liver disease associated with parenteral nutrition.
- Basic or clinical research in small bowel transplantation, either in animal models or humans, that aim to improve multiple aspects of transplantation, including patient selection, transplantation procedures, nutritional support, immunosuppression, and tolerance induction.
- Research to improve diagnosis or treatment of complications of small bowel transplantation, including graft rejection, infections or diarrhea of unknown etiology following transplantation.

DIVISION OF DIGESTIVE DISEASES AND NUTRITION
Conferences and Workshops

Hepatitis C and Renal Disease
Date: October 21-22, 2002
This workshop, co-sponsored by the DDN and KUH Divisions, will assess current knowledge about the relationship between hepatitis C virus (HCV) infection and renal disease and current optimal means of prevention, control and treatment of hepatitis C in patients with kidney disease. Hepatitis C is a cause of renal disease and is also a frequent complication during the management of end-stage renal disease The workshop will be a day-and-a-half meeting that will include oral presentations from 19 national and international speakers on topics of hepatitis C virology, epidemiology, natural history and therapy; incidence of HCV-related renal disease and its natural history; prevalence of HCV infection among patients with end-stage renal disease on dialysis and after renal transplantation; natural history of hepatitis C in patients with renal disease, on dialysis and after transplantation; the problem of renal disease in patients with HCV infection after liver transplantation; prevention of spread of HCV in renal disease patients and therapy of hepatitis C in patients with end-stage renal disease and after renal transplantation. The objective of the meeting is to set a research agenda in the area of hepatitis C and renal disease.

Hepatitis C in Correctional Institutions
Date: January 22-23, 2003
(Co-sponsored by the Centers for Disease Control and Prevention and the Federal Bureau of Prisons)
Hepatitis C is common in prison populations—serosurveys indicate that 20 to 30 percent of male inmates in prison are positive for antibody to hepatitis C. Therapy of hepatitis C is expensive and difficult and provision of care and therapy of hepatitis C to individuals in prisons has been erratic. The Federal Bureau of Prisons has developed a policy for therapy in prisons based upon the NIH Consensus Development Conference statement and the conditions of inmates in prison. This meeting will focus on the size of the problem of hepatitis C behind bars, means of prevention of spread, and ways to provide therapy in the most cost-effective and clinically appropriate manner. Members of the 50 State prison medical systems will be invited to attend this meeting which will have talks on hepatitis C natural history and therapy, epidemiology of hepatitis C in U.S. prisons and jails, experience with therapy of hepatitis C in prisons and focused presentations on the specific problems of treatment of inmates, psychological side effects, need for liver biopsy, means of monitoring, and types of indications and contraindications to therapy and expected outcomes. The purpose of the meeting is to establish a consistent approach to prevention, control and therapy of hepatitis C in U.S. prisons.

Clinical Endpoints for Research in Crohn's Disease
Date: January 13-14, 2003
This meeting will present the results of working group discussions to refine endpoints for clinical trials in Crohn's disease.

Workshop on Obesity Phenotypes for Genetic Studies
Date: To be determined
The Division will organize a two day workshop in FY 2003 at which invited participants will recommend the most suitable obesity-related phenotypes for genetic linkage and association studies.